PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/625,073
Applicant	:	Greene, et al.
Filing Date	:	July 22, 2003
Title	:	METHODS OF INHIBITING OSTEOCLAST ACTIVITY
TC/A.U.	:	1617
Examiner	:	Sahar Javanmard
Attorney Docket No.	:	UPN-5191

September 23, 2008

Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, RAMACHANDRAN MURALI, hereby declare the following:

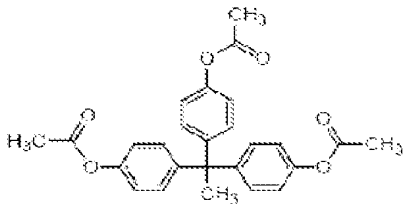
(1) I am a citizen of United States, residing in 131 Dartmouth Av, Swarthmore, Pennsylvania, 19081, and I am a co-inventor of the above identified application.

(2) I received my Bachelor of Science Degree in Physics from the University of Madras, India in 1978 and a Ph.D. Degree in Biophysics from University of Madras, India, in 1986.

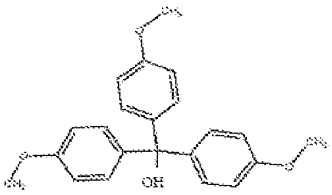
(3) My current position is that of Associate Professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania.

(4) It is my understanding that the pending claims of the above identified application are directed to the use of compounds that are known to be TRANCE/RANK inhibitors for the purpose of inhibiting osteoclastogenesis and/or osteoclast function.

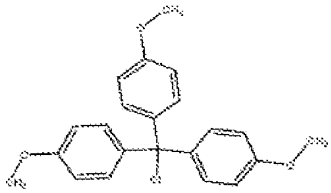
(5) I have personally conducted or been directly responsible for supervision of tests of various TRANCE/RANK inhibitors as inhibitors of osteoclastogenesis and/or osteoclast function. In particular, the following compounds of Formula I, the same as or similar to compounds listed in claim 5 of the application, were tested:



Comp#1

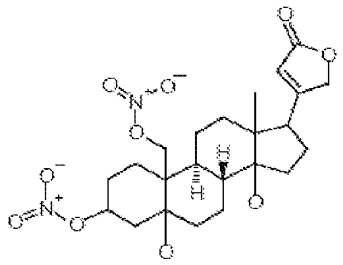


Comp#2

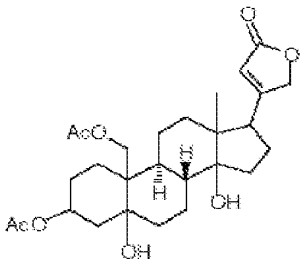


TMT

The following compounds of Formula III, the same as or similar to compounds listed in claim 10 of the application, were also tested:



Comp#1



Comp#2

(6) The test compounds were cultured with cells derived from murine bone marrow, and induced to form oosteoclasts using either TNFalpa or RANKL or both. Briefly, murine bone marrow cells were cultured in 24-well plates at a cell density of $2x10^5$ cells/cm^2 in α-MEM medium containing 10% FBS, 100 units/ml penicillin, 100 μg/ml streptomycin, 30ng/ml CSF-1 and the appropriate concentration of RANK ligand for 4 days, with a change of culture medium on day 3. The cells were then fixed, stained for TRAP, and counted as described in Cheng, X., Kinosaki, M., Takami, M., Choi, Y., Zhang, H. & **Murali, R,** (2004) "Disabling of receptor activator of nuclear factor-kappaB (RANK) receptor complex by novel osteoprotegerin-like peptidomimetics restores bone loss in vivo"

J. Biol. Chem. **279,** 8269-8277. Osteoclast formation was evaluated using the TRAP assay described in Example 2 of the application.

(7) The results are shown in Figures 1 and 2, attached hereto. With regard to test compounds of Formula I, all three compounds inhibited osteoclast formation, with the compounds identified as Compound 1 and TMT (which is referred to as compound I-A in the application) exhibiting excellent correlation between increasing dose and increasing inhibitory effect. Similarly, as shown in Figure 2, the two compounds of Formula III both exhibited dose-dependent inhibition of osteoclast formation.

(8) It is my opinion, in view of these technical results, that one of ordinary skill in the art would readily understand that the claimed TRANCE/RANK inhibitor compounds could be used in the methods of the present invention. In addition, it is my opinion that such an ordinary skilled artisan would be able, without undue experimentation, to select and optimize the use of the claimed compounds, to select a satisfactory route of administration, dosage form and amount to administer, to achieve the desired therapeutic effect, based on the teaching of the present application in combination with the general knowledge and information known or readily available to such artisans.

(9) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 09/26/08

Ramachandran Murali

RAMACHANDRAN MURALI

FIGURE 1

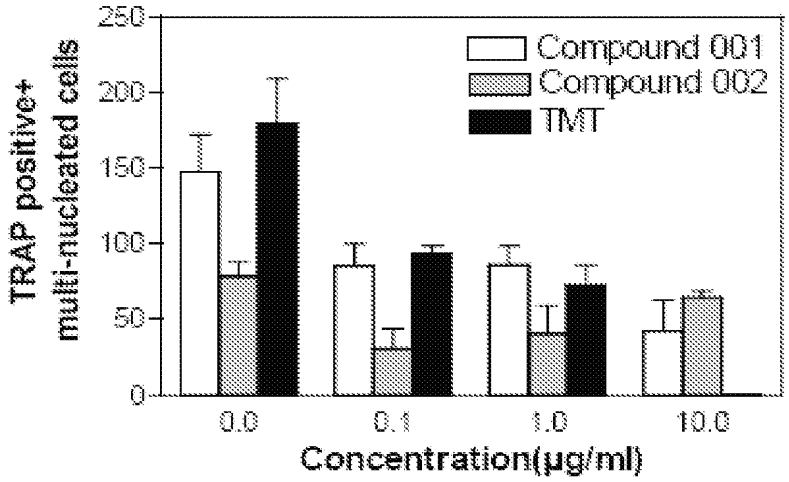


FIGURE 2